INFLAMMATORY MYOPATHIES

Choosing the right biomarkers to predict ILD in myositis

Takahisa Gono and Masataka Kuwana

Interstitial lung disease is one of the most important causes of mortality in patients with polymyositis or dermatomyositis. Understanding the risk factors for development and progression of interstitial lung disease is crucial to improving clinical outcomes.

Refers to Zhang, L. *et al.* Factors associated with interstitial lung disease in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. *PLoS ONE* **11**, e0155381 (2016)

Polymyositis and dermatomyositis are connective tissue diseases characterised by myositis, the presence of myositis-specific autoantibodies (MSAs), and extramuscular complications, such as skin manifestations, interstitial lung disease (ILD) and cardiomyopathy. Although the reported frequency of ILD varies widely (ranging from 20% to 78%), this complication is consistently identified as one of the most important risk factors for mortality in patients with polymyositis or dermatomyositis[1]. A meta-analysis by Zhang *et al.* has identified a number of risk factors associated with the presence of ILD in patients with polymyositis and dermatomyositis[2]. Identification of predictive factors is important for the early recognition of ILD in patients with polymyositis or dermatomyositis in clinical practice, which could lead to improved outcomes.

The speed of progression, treatment response and prognosis are highly variable among patients with polymyositis-associated or dermatomyositis-associated ILD. In these patients, the clinical course of ILD is typically divided into three main forms: rapidly progressive, which progresses over the course of days or weeks and is often refractory to immunosuppressive treatment; acute or subacute, which progresses over the course of weeks or months and responds favourably to immunosuppressive treatment, but frequently recurs after reduction of treatment intensity; and chronic, which is stable during the entire disease course without impairment of pulmonary function. In patients with polymyositis or dermatomyositis, 5-year survival in those with the rapidly progressive, or acute or subacute forms of ILD is much poorer than in those with chronic ILD (52% and 87%, respectively)[3].

The Zhang *et al.* meta-analysis of 23 studies, which included 834 patients, showed that older age at diagnosis of myositis, heliotrope rash, arthritis or arthralgia, fever, the presence of autoantibodies that target either the aminoacyl-transfer RNA synthetase (ARS) Jo-1 or melanoma differentiation-associated gene 5 (MDA5), an elevated erythrocyte sedimentation rate and elevated levels of C-reactive protein were strongly associated with ILD in patients with polymyositis or dermatomyositis. Although a potential limitation of meta-analyses is that cohorts of patients with ILD can differ between studies in terms of ethnic background and disease profiles, Zhang *et al.* adequately adjusted for this selection bias using statistical techniques[2]. These results highlight the need for using high resolution chest CT scans to screen patients with myositis who exhibit one or more ILD risk factors at the time of diagnosis.

> anti-MDA5 antibodies are a useful biomarker for predicting rapidly progressive ILD

Detection of MSAs is useful both for diagnosis of polymyositis and dermatomyositis, and for prediction of clinical characteristics, including the presence, clinical course, response to treatment and prognosis of ILD[4]. The MSAs that are most strongly linked to the presence of ILD are autoantibodies to ARSs (including Jo-1) and to MDA5, with the prevalence of ILD in patients with anti-ARS or anti-MDA5 antibodies being approximately 90%. Other MSAs, such as anti-Mi-2, antibodies that target transcriptional intermediary factor-1α, and antibodies directed against signal recognition particle are not associated, or are even negatively associated, with ILD.

Anti-ARS antibodies are almost always detected in adults with myositis, and are associated with antisynthetase syndrome, a set of clinical manifestations including arthritis or arthralgia, fever, mechanic's hand, Raynaud phenomenon, myositis and ILD. The clinical presentation of patients positive for anti-ARS antibodies of different specificities is similar, but differs in terms of the prevalence of skeletal muscle involvement. Myositis is mainly associated with anti-Jo-1, anti-EJ and anti-PL-7 antibodies, but is less common (7–25%) in patients with other specificities, leading to the diagnosis of clinically amyopathic dermatomyositis, or of ILD with some features associated with anti-ARS antibodies (such as mechanic's hand and Raynaud phenomenon)[5]. In patients with anti-ARS antibodies, ILD develops acutely or subacutely and generally responds favourably to treatment with high-dose glucocorticoids either with or without immunosuppressant drugs. A high prevalence of ILD is common in patients with all anti-ARS specificities[5], raising the idea that anti-ARS antibodies could be regarded as ILD-specific antibodies rather than MSAs. These features are compatible with those of acute or subacute ILD associated with polymyositis or dermatomyositis.

By contrast, anti-MDA5 antibodies are detected in both adults and children with dermatomyositis, and are associated with typical dermatomyositis rashes, cutaneous ulcers, arthritis or arthralgia, fever, amyopathy or hypomyopathy, and rapidly progressive ILD[6]. Since skin lesions are almost always present in patients who are anti-MDA5-positive, very few of these patients are diagnosed with polymyositis[6]. Myopathy is less common in

anti-MDA5-positive patients from Japan than in anti-MDA5-positive patients from Europe, North America, Korea, or even China, but a strong association with rapidly progressive ILD is commonly found in nearly all patient cohorts across ethnic groups[7]. In patients with anti-MDA5 antibodies, rapidly progressive ILD is typically refractory to immunosuppressive treatment, and often leads to a fatal outcome. Moreover, 6-month overall survival is ≤50% in patients with rapidly progressive ILD who are anti-MDA5-positive, although recurrence of ILD after clinical remission in survivors is rarely reported.

In a clinical setting, prompt identification of patients who are likely to develop rapidly progressive ILD and to have a poor outcome is crucial, in order to introduce intensive immunosuppressive treatment as early as possible. High-dose glucocorticoids in combination with calcineurin inhibitors (such as ciclosporin and tacrolimus) and cyclophosphamide are recommended as the first-line treatment, and some evidence suggests that early introduction is essential to achieve good clinical outcomes[8]. Anti-MDA5 antibodies are a useful biomarker for predicting rapidly progressive ILD, and poor prognosis is further correlated with levels of anti-MDA5 antibodies measured by quantitative ELISA and serum levels of ferritin at diagnosis[9].

Heliotrope rash, arthritis or arthralgia, and fever, which were identified as other predictors for the development of ILD by Zhang *et al.*[2], might be explained by the strong association of ILD with both anti-ARS and anti-MDA5 antibodies; however, markers of inflammation, such as elevated erythrocyte sedimentation rate and elevated levels of C-reactive protein, are likely to be independent of the presence of autoantibodies. In this regard, serum concentrations of inflammatory cytokines (such as IL-6, IL-8, and IFNα) and the expression of CD11b mRNA in neutrophils have been associated with a rapidly progressive course of ILD in patients who are positive for anti-MDA5 antibodies[8–10]. Given that a decrease or normalization of these biomarkers is associated with improvements in rapidly progressive ILD and a better prognosis, they might serve as biomarkers for the level of activity of ILD, which could be useful for fine-tuning of immunosuppressive treatment.

In conclusion, physicians need to understand the risk factors for development of ILD in patients with polymyositis or dermatomyositis. Given the heterogeneity of the clinical course of polymyositis-associated or dermatomyositis-associated ILD, the ability to predict disease progression, prognosis, and treatment response is important when making treatment decisions. Among the factors reportedly predictive of the development or poor prognosis of ILD in patients with polymyositis or dermatomyositis, MSAs (including anti-ARS and anti-MDA5 antibodies) are the most reproducible and reliable and should be used in clinical practice.

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Competing interests statement
T.G. declares no competing interests. M.K. is an inventor on US patent application 13/059,444: 'Diagnosis method and diagnosis kit for dermatomyositis'.